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Effects of volatile anaesthetic agents on enhanced airway tone in sensitized guinea pigs

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Background. Although volatile anaesthetics afford protection against bronchospasm, their potential to reverse a sustained constriction of hyperreactive airways has not been characterized. Accordingly, we investigated the ability of halothane, isoflurane, sevoflurane and desflurane to reverse lung constriction induced by prolonged stimulation of the muscarinic receptors in guinea pigs sensitized to ovalbumin.

Methods. Pulmonary input impedance (ZL) was measured using forced oscillations in five groups of ovalbumin-sensitized, mechanically ventilated guinea pigs. ZL was measured under baseline conditions, during steady-state bronchoconstriction induced by an i.v. infusion of methacholine (MCh), and after administration of one of the volatile agents at 1 MAC after the induction of a steady-state bronchoconstriction. Airway resistance (Raw), and parenchymal tissue resistive and elastic coefficients were extracted from ZL by model fitting.

Results. All four volatile agents exhibited an initial relaxation of the MCh-induced airway constriction followed by gradual increases in Raw. The bronchodilatory effect of isoflurane was the most potent (–28.9 (SE 5.5)% at 2 min, $P<0.05$) and lasted longest (7 min); sevoflurane and halothane had shorter and more moderate effects (–21.1 (3.9)%, $P<0.05$, and –6.1 (1.7)%, $P<0.05$, respectively, at 1 min). Desflurane caused highly variable changes in Raw, with a tendency to enhance airway tone.

Conclusions. Volatile agents can reverse sustained MCh-induced airway constriction only transiently in sensitized guinea pigs. Isoflurane proved most beneficial in temporally improving lung function in the presence of a severe constriction of allergic inflamed airways. Desflurane displayed potential to induce further airway constriction.

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There has recently been a worldwide increase in the recognition of patients with bronchial hyperreactivity (BHR) who, with an elevated perioperative respiratory morbidity, pose challenges to the anaesthetist.[1 2] The fact that most anaesthetic agents have bronchoactive properties compels anaesthetists to select an optimal anaesthetic management in this population, which is at high risk of enhanced lung constriction.

Among the anaesthetic drugs, volatile inhalation agents are expected to possess beneficial properties, since numerous studies have demonstrated their potential to prevent lung constriction.[3–12] However, only a few studies have addressed the ability of volatile agents to reverse a sustained lung constriction.[7 13 14] Brown and colleagues[7] and Hashimoto and colleagues[14] made use of a continuous i.v. infusion of histamine to induce steady-state bronchoconstriction, and described dose-dependent gradual increases in airway diameter during the administration of halothane,[7 14] enflurane,[14] isoflurane[7] and sevoflurane.[14] Nevertheless, tachyphylaxis may have been involved in the observed

airway dilation, as the level of lung constriction has been shown to decrease during prolonged infusion of histamine.[15] Ishikawa and colleagues[13] infused methacholine (MCh) to generate steady-state changes in lung mechanics without separating airway and parenchymal effects. Since the MCh infusion was likely to generate both airway and parenchymal constriction in their animals,[16] changes in airway mechanics could not be characterized. Additionally, all these previous studies on the preventive or reversal effects of volatile anaesthetics involved animals with normal lung reactivity. Thus, the effects of these inhalation agents on constricted sensitized airways have not yet been investigated.

We used an animal model of BHR to characterize the ability of the routinely used volatile inhalation agents (halothane, isoflurane, sevoflurane and desflurane) to reverse lung constriction induced by prolonged stimulation of muscarinic receptors. Since BHR affects primarily the airways, a forced oscillation technique at low frequencies[12 15–20] was applied to separate airway and tissue properties for an accurate description of changes in the lungs.

Methods

Sensitization

To induce BHR, young male, pathogen-free Hartley guinea pigs weighing 250–350 g were actively sensitized by daily exposure to aerosolized ovalbumin (10 mg ml^{-1} in sterile sodium chloride 0.9% solution for 5 min) for a period of 1 week.[21 22] In order to avoid the development of tolerance to ovalbumin, the animals were fed with food free of egg proteins, and were kept under environmental conditions that were as stable as possible. Food and water were available *ad libitum*.

Animal preparation

Guinea pigs were anaesthetized with urethane 2 g kg^{-1} i.p. This dose produces deep anaesthesia for 8–10 h.[23] A tracheostomy was then performed and the guinea pigs were mechanically ventilated (Model 683, Harvard Apparatus, South Natick, MA, USA) with a constant tidal volume of 1 ml 100 g^{-1} and a frequency of 50–60 min^{-1} at an FI_{O_2} of 0.3 in air. The femoral artery was cannulated with a silastic catheter (28-gauge catheter, Portex, Hythe, UK) for continuous haemodynamic monitoring (arterial pressure and heart rate) with a calibrated pressure transducer (model 156 PC 06-GW2, Honeywell, Zürich, Switzerland). A similar silastic catheter was inserted into the jugular vein for drug delivery. Fentanyl was administered at 2 μg kg^{-1} h^{-1} to ensure adequate analgesia. A thoracotomy was performed with sternal splitting and the chest was largely retracted. A positive end-expiratory pressure of 2.5 cm H_2O was applied to avoid lung collapse.

Airway pressure was measured continuously using a calibrated pressure transducer (Validyne DP 45, Northridge, CA, USA). Rectal temperature was monitored with a temperature sensor (Thermalert, model TH-8, Physitemp, Clifton, NJ, USA) and maintained at 37 (0.5)°C with a heating pad (Miostar, Zürich, Switzerland). Airway and arterial pressures, heart rate and rectal temperature were displayed and stored on a microcomputer at a sampling rate of 50 Hz via an analogue/digital interface converter (Biopac, Santa Barbara, CA, USA).

Arterial blood samples were analysed radiometrically (model 505, Acid Base Laboratory, Copenhagen, Denmark) before each MCh challenge. End-tidal concentrations of oxygen, carbon dioxide and volatile agents were monitored throughout the study (UltimaTM, Datex/Instrumentarium, Helsinki, Finland). The volatile agents were administered by a vaporizer connected to the ventilator inlet. Target end-tidal concentrations of volatile agents were achieved in a short period of time (within 1 min) because of the low dead space of the ventilation circuit, the high ventilation rate in guinea pigs, and the relatively high fresh gas flow. The vaporizer was adjusted if necessary to ensure a constant 1 MAC end-tidal volatile anaesthetic concentration.

Measurement of airway and tissue mechanics

The respective contributions of the airway and tissue mechanical properties to total lung resistance were estimated by the forced oscillation technique by measuring pulmonary input impedance (ZL), as described in detail previously.[12 17] Briefly, the tracheal cannula was connected from the respirator to a loudspeaker-in-box system at end-expiration. The loudspeaker generated a small-amplitude pseudo-random signal with frequency components of 0.5–21 Hz through a polyethylene wave tube with known geometry. Two identical pressure transducers were used to measure the lateral pressures at the loudspeaker (P_1) and at the tracheal end (P_2) of the wave tube. ZL was calculated as the load impedance of the wave tube using fast Fourier transformation:

$$ZL = Zo \sinh(\gamma L)/[(P_1/P_2) - \cosh(\gamma L)]$$

where L is the length, Zo is the characteristic impedance and γ is the complex propagation wave number of the wave tube. The latter two parameters are determined by the geometrical data and the material constants of the tube wall and the air. To separate the airway and tissue mechanics, a model containing a frequency-independent airway resistance (Raw) and inertance (Iaw) in series with a constant-phase tissue model[16] including parenchymal damping (G) and elastance (H) was fitted to the ZL spectra by minimizing the differences between the measured and modelled impedance values:

$$ZL = Raw + j\omega Iaw + (G - jH)/\omega^{\alpha}$$

Table 1 Relative changes in airway resistance (Raw), inertance (Iaw), parenchymal damping (G) and elastance (H) during methacholine (MCh)-induced steady-state constriction before the onset of the volatile agent

	Halothane (*n*=10)	**Isoflurane (*n*=10)**	**Desflurane (*n*=7)**	**Sevoflurane (*n*=7)**	**MCh alone (*n*=5)**	**One-way ANOVA**
Raw (%)	130 (28)	90 (24)	122 (38)	159 (56)	138 (43)	*P*=0.31
Iaw (%)	–40 (10)	–22 (7)	–48 (17)	–44 (31)	–47 (20)	*P*=0.77
G (%)	56 (19)	31 (9)	46 (13)	82 (40)	114 (52)	*P*=0.51
H (%)	15 (7)	12 (4)	8 (6)	13 (8)	23 (10)	*P*=0.67

where j is the imaginary unit, ω is the angular frequency ($2\pi f$), and $\alpha=2/\pi \arctan(H/G)$.

Experimental protocol

Fifty-two guinea pigs were included in the study. No sensitization was performed on eight, while the other 43 were exposed to ovalbumin. After surgery, a period of 5–10 min was allowed to establish steady-state conditions, and four baseline ZL recordings were collected. The i.v. MCh infusion was then started (1 μg kg^{-1} min^{-1}). Ten min later, when the constriction was expected to be in a steady state, ZL was measured at 1 min intervals for 5–10 min, until four successive measurements revealed the same lung mechanical condition. If the estimated airway response was lower than 25%, the rate of infusion of MCh was increased to 2 or 4 μg kg^{-1} min^{-1} and ZL was collected for another 10 min. The guinea pigs were then randomly assigned to receive no volatile anaesthetic (*n*=5) or halothane (*n*=10), sevoflurane (*n*=7), isoflurane (*n*=10) or desflurane (*n*=7) at a concentration of 1 MAC. MAC values for the guinea pigs were established as 1% for halothane,[24] 1.2% for isoflurane,[24] 6.4% for desflurane[25] and 2% for sevoflurane.[26] Changes in lung mechanics during gas administration were followed by measuring ZL at 1 min intervals for 10 min. Administration of volatile agent was then terminated and a period of 8 min was allowed before another four ZL data sets were collected, while MCh was maintained.

To ensure the efficacy of the sensitization procedure, a new set of control ZL measurements were collected after the MCh infusion, and ovalbumin 0.2 mg was injected i.v. The resultant effect of the antigen–antibody reaction on the early-phase lung response was estimated by collecting ZL data for a further 4 min.

Bronchoalveolar lavage (BAL) fluid was collected at the end of the experiment by introducing normal saline under a hydrostatic pressure of 20 cm H_2O into the trachea. The extracted 10–20 ml BAL fluid was immediately centrifuged for 10 min at 1600 rpm while a temperature of 4°C was maintained. The sedimented cells were mixed with 1 ml of phosphate-buffered saline. Total and differential cell counts were performed on cytospin slides, standard morphologic criteria being applied.

BHR was assessed by comparing the changes in lung mechanical parameters during infusion of MCh 1 μg kg^{-1} min^{-1} in non-sensitized animals (*n*=8) and in those undergoing the sensitization procedure and receiving the same dose of MCh (*n*=19).

ZL data collected under baseline conditions and those measured during steady-state constriction were averaged and used for model fitting. Individual ZL data were fitted with the model during administration of the volatile agent, and following ovalbumin challenge. In the latter case, peak response in Raw was used for further analyses.

Statistical analysis

Scatters in the parameters were expressed in SE values. The Kolmogorov–Smirnov test was used to test data for normality. Changes in the lung mechanical parameters in response to MCh or ovalbumin in naive and sensitized animals were compared using *t*-tests. The temporal effects of the volatile agents were assessed by using repeated-measures one-way analysis of variance (ANOVA). Another one-way ANOVA was applied to compare the effects of the different volatile agents at a given time point. Pairwise comparisons were performed using Student–Newman–Keuls multiple comparison procedures. Statistical significance was set at $P<0.05$.

Results

Sensitization induces BHR

Among the 43 sensitized animals, daily exposure to an ovalbumin aerosol induced respiratory distress in six guinea pigs on day 7, necessitating the suspension of ovalbumin administration, and oxygen and salbutamol administration. Despite this respiratory support, four guinea pigs died during the sensitization period; these animals were excluded from the protocol groups.

Analyses of BAL revealed that sensitization resulted in statistically significant increases in the relative numbers of neutrophils (102 (14)% compared with those in naive animals (52 (14)%, $P<0.05$). The number of monocytes/macrophages was also higher in sensitized than untreated animals (158 (29) *vs* 101 (8), $P<0.05$).

In sensitized animals, baseline lung mechanical parameters were similar to those observed in the non-sensitized animals (31.5 (1.7) *vs* 31.9 (1.2) cm H_2O s $litre^{-1}$ for Raw, 232 (11) *vs* 242 (10) cm H_2O $litre^{-1}$ for G, and 1084 (70) *vs* 994 (42) cm H_2O $litre^{-1}$ for H. A MCh infusion 1 μg kg^{-1}

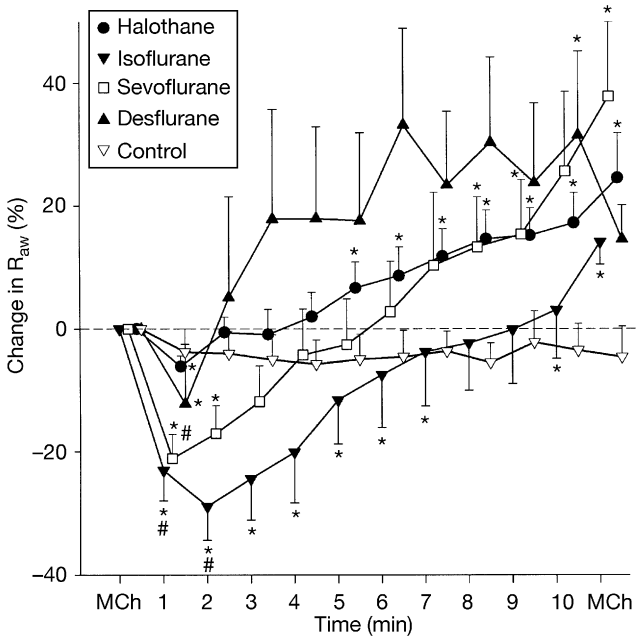

Fig 1 Changes in airway resistance (Raw) during volatile agent administration. Values (mean and SE) are represented as relative changes from the plateau constriction induced by continuous infusion of methacholine (MCh). *P<0.05 *vs* the Raw value obtained at the MCh plateau for a given volatile anesthetic. #P<0.05 *vs* the Raw value obtained in the control group at the corresponding time point.

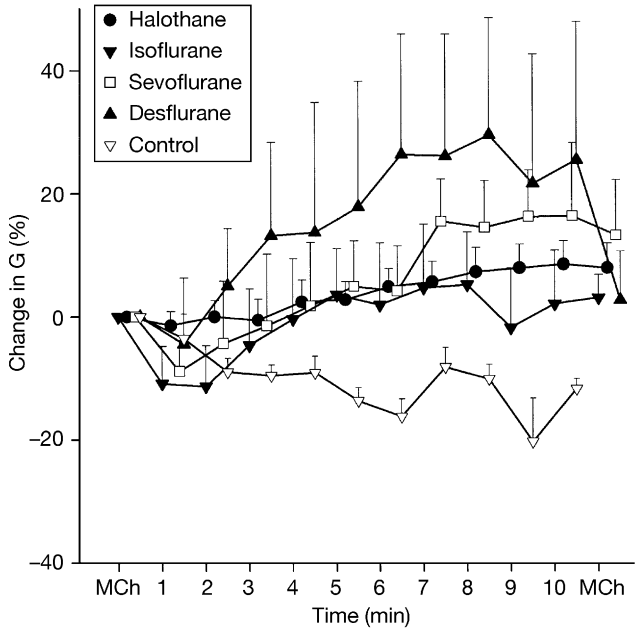

Fig 2 Changes in tissue damping coefficient (G) during volatile agent administration. Values (mean and SE) are represented as relative changes from the plateau constriction induced by the continuous infusion of methacholine (MCh).

min^{-1} into animals sensitized with ovalbumin induced significantly greater elevations in Raw (150 (28)%) and G (65 (16)%) than those in the non-sensitized group (16 (8)%, P=0.005, and 1.4% (3.1)%, P=0.01). H increased only slightly in both groups of guinea pigs (21 (6)% *vs* 7 (6)%, P=0.17). I.V. administration of ovalbumin 0.2 mg induced an early-phase type response only in the sensitized animals. This response was observed in all the sensitized animals included in the present study, with a severe reaction leading to complete airway obstruction and circulatory collapse in three animals. In the animals in which data collection was completed, peak increases in Raw, G and H were 418 (87)%, 831 (297)% and 258 (92)%, respectively.

Effects of methacholine

Similarly to previous findings,[12 17] the i.v. MCh infusion induced marked and statistically significant elevations in Raw and G, while the increases in H were smaller. Furthermore, there was no difference between the protocol groups in the magnitude of the MCh-induced changes in lung mechanical parameters (Table 1).

Effects of volatile agents

Figure 1 illustrates the effects of the volatile anaesthetic agents on MCh-induced increases in Raw. All four volatile anaesthetics caused statistically significant decreases in Raw after 1 min administration. Isoflurane was the most potent in reversing the MCh-induced bronchospasm. Moreover, the bronchodilatory effect of isoflurane was the most marked (–28.9 (5.5)% at 2 min, P<0.05) and lasted the longest (7 min). Sevoflurane also decreased Raw markedly (21.1 (3.9)% at 1 min, P<0.05) with a bronchodilatory duration of only 2 min. A bronchodilatory effect was observed for halothane (6.1 (1.7)%, P<0.05) and desflurane (12.2 (9.7)%, P<0.05) only after the first min of inhalation. After this initial bronchodilatory effect, a trend was observed in Raw to increase for all gases. Significant increases in Raw were observed after 5 min for halothane, 8 min for sevoflurane and 10 min for isoflurane. Prolonged administration of desflurane caused highly variable changes in Raw: marked increases in Raw were observed in four guinea pigs, whereas in the other animals the long-term changes in Raw followed a qualitatively similar trend to those observed for the other gases. On termination of inhalation agents, MCh induced a further increase in Raw in those animals that had received halothane, isoflurane or sevoflurane.

Figures 2 and 3 demonstrate the effects of these volatile anaesthetics on the tissue resistive and elastic properties, respectively. Changes in G during volatile agent administration followed patterns similar to those observed in Raw, but the effects were smaller, and hence a statistically significant difference was not detected. In general, the volatile agents had minor effects on H.

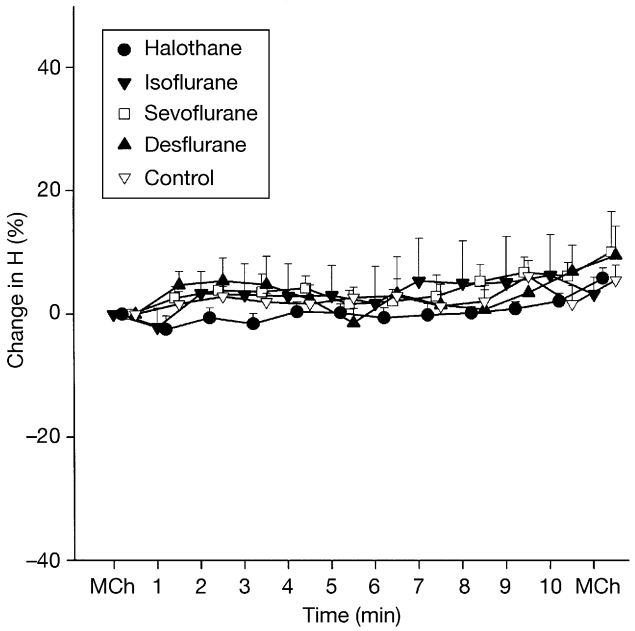

Fig 3 Changes in tissue elastance (H) during volatile agent administration. Values (mean and SE) are represented as relative changes from the plateau constriction induced by the continuous infusion of methacholine (MCh).

Discussion

The present investigation related the ability of routinely used volatile anaesthetic agents to reverse the bronchoconstriction induced by stimulation of muscarinic receptors in the presence of BHR. An initial bronchodilatory effect followed by a gradual deterioration in airway function was observed during the administration of halothane, sevoflurane or isoflurane. Desflurane anaesthesia was associated with a significant interindividual variability, with a tendency to aggravation of bronchoconstriction.

Methodological issues

In accordance with previous studies,[21 22] repeated sensitization with ovalbumin induced BHR in response to MCh and resulted in an antigen–antibody reaction with severe lung constriction. The total number of leucocytes in the BAL fluid collected from the sensitized animals was significantly higher than that in the control animals, indicating that airway inflammation was induced by airway sensitization. This model of BHR was chosen because it mimics the clinical situation where anaesthetists must meet the challenge of the management of patients with bronchial inflammatory disease leading to hyperreactive airways.

Direct stimulation of the muscarinic receptors is frequent in clinical practice, particularly during tracheal intubation or mechanical stimulation of the airways (i.e. bronchoscopy or bronchial suction). The muscarinic receptors can also be activated following acetylcholine liberation via vagal stimulation (i.e. surgical stimulation under light anaesthesia, and manipulation of the upper airways). Accordingly, MCh was chosen to mimic these situations encountered in clinical practice. Moreover, since identification of airway behaviour following muscarinic stimulation is of primary interest for anaesthetists, the i.v. administration of MCh was chosen because this route has been shown to lead primarily to bronchoconstriction in small rodents without alterations in the viscoelastic properties of the lung parenchyma.[12 17 18] In agreement with our previous findings in rats,[12 17] i.v. MCh infusion also predominantly induces airway constriction in this animal model. The moderate increases in G observed in the present study without significant changes in H reflect enhanced ventilation heterogeneities.[18]

As most previous studies used global parameters to characterize the lung responses to volatile anaesthetic agents,[3 4 6–9 13] the relative contributions of the airways and the parenchyma to the lung response cannot be distinguished. In the present study, forced oscillatory impedance data were used to separate airway and parenchymal mechanics. This technique has been validated[17 18] and applied successfully in small rodents.[12 19 20] The impedance data obtained in the present study are in good qualitative agreement with those measured in various mammals,[10 12 15–18] and are similar to the ZL data obtained previously in guinea pigs.[19 20] Furthermore, the comparable lung mechanical parameters under baseline conditions in the controls and sensitized guinea pigs confirm the previous finding that sensitization does not alter baseline lung mechanics, affecting only airway responsiveness to constrictor stimuli.[22]

Effects of volatile agents

This is the first study demonstrating a temporal change after the administration of volatile agents in the presence of sustained airway constriction in an animal model of BHR. All the volatile agents tested exerted a bronchodilatory effect, with different magnitudes and timings, which gradually declined with time.

Isoflurane had the most potent bronchodilatory effect, and lasted longest among the agents studied at comparable alveolar concentrations. This potential of isoflurane to reverse bronchoconstriction is in accordance with previous clinical and experimental observations.[7–9]

After the very transient decreases in Raw observed at 1 min with desflurane, this volatile agent induced highly variable changes in Raw, with a mean increase of approximately 20%. This finding confirms recent results by Goff and colleagues,[27] which demonstrated a significant bronchoconstriction in patients with BHR when desflurane was administered after tracheal intubation.

The bronchodilatory effect vanished in the second phase of volatile agent administration; indeed, further increases in Raw were observed. This effect was the most noteworthy for halothane and sevoflurane, whereas the deep initial

decrease in Raw during isoflurane administration led to significant increases only at the end of the administration period. Since the end-tidal concentration of volatile agent was monitored continuously and the vaporizer was adjusted accordingly, stable anaesthetic levels were guaranteed. Furthermore, the instability of a sustained MCh infusion is not responsible for this finding either, since MCh induced stable increases in Raw in the guinea pigs receiving no volatile anaesthetic (Fig. 1). To explain the decline in the bronchodilatory potential of the volatile agents, the mechanisms of their action on the tracheobronchial tree needs to be considered.

The direct effect of volatile anaesthetics on airway smooth muscle can be excluded, since the constrictor effects of the volatile agents would be expected to decline once their administration is terminated. Since the bronchodilatory capabilities of volatile agents on the distal bronchi are mediated by the epithelium,[28] epithelial damage induced by sensitization[29] may have altered epithelial function, leading to the lack of a persistent bronchodilation. Augmentation of inflammatory reactions in the sensitized airways caused by volatile anaesthetics[30] may have also led to the increases observed in Raw. However, this phenomenon was not likely to play a major role, since our additional experiments in animals with normal and hyperreactive airways revealed similar effects of volatile anaesthetics on basal airway tone (0.3 (4.4)% *vs* 7.0 (5.7)% decrease in Raw 10 min after isoflurane administration in the control and sensitized guinea pigs, respectively; P=0.33). To induce liberation of pro-inflammatory cytokines by volatile agents in animals with hyperreactive airways, a longer period of inhalation anaesthesia and mechanical ventilation may be necessary.[30]

The indirect effects of the volatile agents, such as involvement of neural or humoral pathways or interactions between pulmonary haemodynamics and airway mechanics, may also have contributed to the decline in bronchodilatory potential. To clarify the role of altered haemodynamics, it is noteworthy that there were no statistically significant additional changes in haemodynamic parameters (arterial pressure and heart rate) after introduction of the volatile agents (data not shown), which makes it unlikely that this mechanism contributed to the elevations in Raw. To investigate the potential role of the vagus, further experiments in another group of sensitized, vagotomized guinea pigs also revealed the same biphasic changes in Raw (data not shown). This finding suggests that vagal reflexes are not responsible for this phenomenon. Thus, other indirect mechanisms via either the non-adrenergic non-cholinergic neural pathway or release of different bronchoactive humoral mediators, or both, may have gradually overcome the direct dilatory effects of the volatile agents.[31] To identify the underlying mechanisms, further experiments involving the use of different blocking agents in a large number of animals would be required and would be a subject of subsequent investigations.

Summary and conclusions

Volatile agents exert a potent bronchodilatory effect in providing protection against constrictor stimuli. The present study demonstrated that inhalational anaesthetics exhibit only a transient dilatory activity in the presence of a sustained constriction in an experimental model of bronchial hyperreactivity. Isoflurane was found to be the most effective in decreasing elevated airway tone, whereas desflurane displayed a potential to induce further airway constriction. Prolonged administration of all volatile agents led to a decline in bronchodilatory potential via indirect effects. These findings confirm the advantage of isoflurane in the presence of bronchospasm and the potential risk of a further increase in airway tone when desflurane is administered to hyperreactive airways.

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